

REMARKS/ARGUMENTS

I. Claim Amendments

Applicants have amended claim 1 to remove any reference to major depressive disorder. No new matter is added by the amendment. Applicants have also canceled claims 52-53. New claim 56 has been added which depends from claims 1 and 54 and recites an additional step of treating the subject following a determination of bipolar disorder. Support for claim 56 may be found in the specification at, e.g., pages 47-55, as well as in the common knowledge of those skilled in art of treating subjects suffering from bipolar disorder. Thus, claim 56 does not constitute new matter.

II. Response to Rejection Under 35 U.S.C. § 112, 1st Paragraph

On page 2 of the Office Action, the Examiner rejected claims 1 and 51-55 as non-enabled under 35 U.S.C. § 112, 1st paragraph. Specifically, the Examiner wrote that the specification was "enabling for a method of diagnosing bipolar disorder as recited by measuring TBR1 mRNA in the dorsolateral prefrontal cortex," but was not enabling for a method of diagnosing major depression disorder by measuring TBR1 mRNA or CAMKII- α mRNA. *See* Office Action at page 2. Upon entry of the present amendment, Applicants' claim 1 recites only the subject matter that the Examiner has indicated is enabled. Applicants therefore respectfully request withdrawal of the Examiner's enablement rejection with respect to claims 1 and 51.

On pages 3-4 of the Office Action, the Examiner argues that

with regard to CAMKII expression and bipolar illness, the prior art suggests that CAMKII actually decreases in the dorsal lateral prefrontal cortex of bipolar patients (Xing *et al.* 2002). Therefore, the prior art indicates measuring CAMKII mRNA is unpredictable as a marker for bipolar illness. . . . The specification provides examples that indicate expression . . . CAMKII is NOT significantly changed in patients with major depression (*sic*).

(emphasis added) Applicants respectfully submit that the Examiner's arguments fail to address the data in Applicants' specification plainly showing that both TBR1 and CAMKII- α are biomarkers whose upregulation is useful for diagnosing bipolar disorder. Specifically, the data showing that CAMKII- α is upregulated in the DLPFC of bipolar subjects appears in Figure 5 and is discussed at paragraph 214 of the specification (page 59). The data show a clear and significant increase in CAMKII- α mRNA levels in the DLPFC of bipolar subjects relative to controls.

Applicants acknowledge that the Xing *et al.* reference cited by the Examiner describes results that apparently contradict the data presented in Applicants' specification. Applicants respectfully submit, however, that the results of Xing *et al.* are not reliable, mainly because the quality of the tissue samples chosen by Xing *et al.* (*i.e.*, samples from the Stanley Foundation collection of human brains) can lead to spurious findings in case-control comparisons. Specifically, Torrey *et al.* (2000; attached) evaluated the Stanley Foundation brain collection and showed an average pH of 6.1 - 6.3. *See* Torrey *et al.* at Table 1. Applicants and others have demonstrated that this range is below the optimal pH for this kind of study. *See, e.g.*, Li *et al.*, (attached) 2004 (page 613, top of righthand column).

The brains used to generate the data in Applicants' specification were part of a large microarray analysis that has resulted in several published papers in well-respected, peer-reviewed journals. *See, e.g.*, Evans *et al.* (2004); Choudary *et al.* (2005), attached. The two genes recited in the pending claims were selected only after a comprehensive evaluation of the integrity of the RNA samples obtained from the brains. Applicants typically evaluate more than 1,200 brains a year, based on a set of rigorous screens including pH tests, before settling on 30-50 specimens that are ideal for analysis. For all the forgoing reasons, Applicants respectfully request withdrawal of the Examiner's enablement rejection under 35 U.S.C. § 112, 1st Paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Chris J. Ullsperger
Reg. No. 48,006

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
CJU:jc
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